IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 8202**
Hashime KANAZAWA et al.	:	Attorney Docket No. 2005_0741A
Serial No. 10/533,806	:	Group Art Unit 1625
Filed May 5, 2005	:	Examiner Rita J. Desai
PYRAZOLONAPHTHYRIDINE DERIVATIVES	:	**Mail Stop: AMENDMENT**

RESPONSE TO NON-FINAL REJECTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

Sir:

The following is responsive to the Office Action of October 14, 2008, the time for responding thereto being extended for three months in accordance with the fee for the Extension of Time submitted herewith. Applicants submit the following remarks in support of the patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims. Further and favorable reconsideration is respectfully requested in view of these remarks.

Rejection Under 35 U.S.C. § 103(a)

The rejection of claims 1 and 5 under 35 U.S.C. § 103(a) as being unpatentable over EP '840 and US '610 is respectfully traversed.

The Position of the Examiner

(1) The Examiner indicates that Applicants' previous arguments are not persuasive for the following reasons.

(1-1) The Examiner indicates that the comparative data in the (previously filed) Declaration indicates that the results were conducted using the Nicholson et al. Method, which differs from the cited art using the Probit Method.

(1-2) Further, the Examiner refers to EP '725 as teaching a range in IC_{50} data of from 0.06

to 2.2, which shows a variation of up to four times. Therefore, the Examiner takes the position that Applicants' results are not unexpected.

(2) The Examiner maintains the obviousness rejection for the following reasons. [These are the Examiner's assertions, and Applicants do not acquiesce to these positions.]

(2-1) Applicants' Declaration does have some data for one compound, just the phenyl, although the prior art has a **thienyl** group and an **alkyl** group.

(2-2) The prior art compounds have the same bronco dilatory effect.

(2-3) Applicants' Declaration does not compare all of the closest art compounds.

(2-4) EP '725 (WO 01/42244) discloses the A group on a similar naphthyridin-2(1H)-one derivative, which is a PDE IV inhibitor, and has a methylene group with the A substituent. Thus, motivation to modify the US '610 compound can also come from the teaching of EP '725, which has the substituent similar to the one at the 3-position.

Applicants' Arguments

(3) Evaluation Method for PDE Activities (Item (1-1))

PDE inhibition was evaluated by the Nicholson et al. Method with reference to the Probit Method, as described in the Examples of the description (page 33, line 7 to page 34, line 7) and in EP '725 (paragraphs [0045]-[0047]). These descriptions may confuse the relation between the Nicholson et al. Method and the Probit Method.

However, as is apparent from these descriptions (see the above paragraphs), the assay for evaluating PDE activities was conducted according to Nicholson et al. Method, and Probit Method was used only for calculating IC_{50} (the concentration of the test compound required for 50% inhibition). Therefore, there is no inconsistency in the evaluation method of PDE activities.

(4) Modification of US '610 compound with EP '725 (Item (2-4))

(4-1) Chemical Structures of the Compounds in the Cited Art

US '610 (Suzuki et al.):

US '610 discloses a pyrazolonaphthyridin derivative in which R^2 (lower alkyl, thienyl, aryl and so on) is substituted on the pyrazole ring which is peri-condensed at the 3- and 4-positions of

the naphthyridin-2(1H)-one skeleton.

EP '725 (WO 01/42244, Aotsuka et al.):

EP '725 discloses a naphthyridin-2(1H)-one derivative having the A group on the 3-position of the naphthyridin-2(1H)-one skeleton via an alkylene group $(CH_2)_m$ in the form of "-$(CH_2)_m$-A", as recited in the claims.

(4-2) Combination of the Compounds recited in Cited Art

Combination of the compounds recited in the cited art references according to the Examiner's comments might have motivated a naphthyridin-2(1H)-one derivative, since the compounds of the references have the naphthyridin-2(1H)-one skeleton.

However, the compounds of US '610 have the substituent R^2 on the pyrazole ring of the pyrazolonaphthyridine backbone. On the contrary, the compounds of EP '725 have -$(CH_2)_m$-A on the naphthyridine backbone. Thus, the basic skeleton of the compounds of US '610, the pyrazolonaphthyridine, is significantly different from that of EP '725, the naphthyridine.

Further, bronco dilatory activity cannot be expressed by only the pyrazolonaphthyridine skeleton of US '610, or by only the naphthyridine skeleton of EP '725, as is apparent from the fact that R^1 and R^2 are essential for the compounds of US '610, and -$(CH_2)_m$-A is essential for the compounds of EP '725. That is, in order to express bronco dilatory activity, R^1 and R^2 should be combined on the pyrazolonaphthyridine skeleton in US '610, and the group -$(CH_2)_m$-A is combined on the naphthyridine skeleton in EP '725, and these elements of the compounds cannot be independent from each other. Particularly, the compound of US '610 has had R^2 at the 3-position of the pyrazolonaphthyridine skeleton, and therefore there is no motivation for combining the pyrazolonaphthyridine skeleton with the group -$(CH_2)_m$-A.

Furthermore, R^2 of US '610 represents H, lower alkyl, thienyl, aryl, OH, and NH_3, while "-$(CH_2)_m$-A" of EP '725 represents -$(CH_2)_m$-heteroaryl group or -$(CH_2)_m$-fused benzene-heteroaryl ring. There are no common substituents between R^2 of US '610 and "-$(CH_2)_m$-A" of EP '725. Therefore, one of ordinary skill in the art would not replace the R^2 on the pyrazole ring of the compounds in US '610 with a group -$(CH_2)_m$-A of the compounds in EP '725.

Even if the US '610 compound is modified with the group "-$(CH_2)_m$-A" of EP '725, Applicants' claimed compounds could not be obtained, since the A group is a heteroaryl group or a fused benzene-heteroaryl group.

Accordingly, one of ordinary skill in the art would not have been motivated to modify the US '610 compound with EP '725, since the basic skeletons of US '610 and EP '725 are significantly different, each of compounds of US '610 and EP '725 is composed of elements which cannot be separable from each other, and there is no replaceability between R^2 in US '610 and -$(CH_2)_m$-A in EP '725.

(5) Applicants' Invention Provides Unexpected Results

(5-1) Variation in IC_{50} data in EP '725

(a) The Examiner points out that EP '725 teaches IC_{50} data from 0.06 to 2.2, which is a four times variation.

(b) However, it should be noted that the claimed subject matter defines only two specific compounds, since A is a phenyl or a fluorine-substituted phenyl; R^1 is hydrogen; R^2 is hydrogen; and m is 1.

On the contrary, IC_{50} of 0.06 in EP '725 is provided by Example No. 6 (A = pyridine-4-yl, m=2, R^2=3-nitro) and IC_{50} of 2.2 in EP '725 is provided by Example No. 17 (A=pyridine-3-yl, m=5, R^2=3-nitro). It should be understood that EP '725 only shows the dependency of inhibition of PDE isoenzymes (IC_{50}) by these substituents.

Therefore, there is no basis for comparing the effects between the claimed subject matter with EP '725.

(5-2) The 2nd Declaration Under Rule 1.132

In order to prove the unexpected results of the claimed subject matter, Applicants have conducted further experiments. [In addition to those presented in the Declaration filed November 15, 2007.] That is, as the present compounds, a compound having a benzyl group (R^2 = benzyl group (R^2 of Declaration formula); or m =1 and A = phenyl group (m and A of the claim formula)) was prepared in accordance with Example 9 (Compound A). [Please note that R^2 in the Declaration is distinct from R^2 in the claims. Please see the formula on page 4 of the enclosed

Declaration.]

On the contrary, as the closest compounds, Applicants prepared each of Compounds 1 (R^2 = phenyl group), 2 (R^2 = methyl group), 10 (R^2 = thienyl group) and 13 (R^2 = 4-fluorophenyl group) of US '610 as Compounds B, C, D and E, as shown in the Declaration.

The test compounds A-E were used for evaluating inhibitory effects in IgE-dependent ear swelling response model mice. The results are summarized in the following Table.

Table

Test Compounds	Compound A	Compound B	Compound C	Compound D	Compound E	Control
R^2	benzyl	phenyl	methyl	thienyl	4-fluorophenyl	
ΔT Mean ± SE	13.8±1.2	17.8±0.8	22.0±0.4	23.2±0.7	21.0±1.3	25.0±0.6
Inhibitory Rate (%)	44.8%	28.8%	12.0%	7.2%	16.0%	-
Significant Difference (vs Control)	p<0.01 (**)	p<0.01 (**)	p<0.05 (*)		p<0.05 (*)	
Significant Difference (vs Compound A)		p<0.05 (*)	p<0.01 (**)	p<0.01 (**)	p<0.01 (**)	

In the table, ΔT means the right ear swelling.

In the column "Significant Difference (vs Control)", the symbol "**" represents $p<0.01$ and the symbol "*" represents $p<0.05$ against control in the significant difference assay.

In the column "Significant Difference (vs Compound A)", the symbol "**" represents $p<0.01$ and the symbol "*" represents $p<0.05$ against the Compound A in the significant difference assay.

As apparent from the Table, Compound A shows a significant inhibitory effect (44.8%), and suppresses allergic inflammation in comparison with Compounds B to E, with a significant difference $p<0.05$ (the symbol "*") and $p<0.01$ (the symbol "**") in the right ear swelling (ΔT). These effects are remarkable and unexpected by the cited references.

For these reasons, the invention of the claims is clearly patentable over the cited combination of references. Applicants respectfully request withdrawal of the above-rejection.

Conclusion

Therefore, in view of the foregoing remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Response, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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